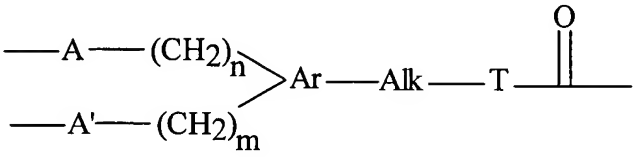
where A and A' define a respective ester linkage between an hydroxy on the linker and the carboxy on R_1 or R_2 or an ester linkage between a carboxy on the linker and the hydroxy on R_1 as a fatty alcohol, or an amide linkage between an amine on the linker and a carboxy on R_1 or R_2, or an amide linkage between a carboxy on the linker and an amine on R_1 or R_2, or one of A and A' is as defined and the other is hydroxy, amino or carboxy in the event that R_1 itself is a free hydroxy, amino or carboxy group.--

B1 Cont.

Please replace the paragraph beginning on page 6, line 1, with the following rewritten paragraph:

--



IIb

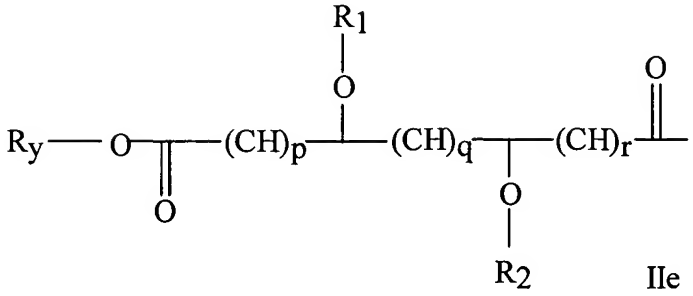
B2

where Ar is a saturated or unsaturated, preferably monocyclic carbo- or heterocycle with 5 or 6 ring atoms; and

A, A', T, Alk, m and n are as defined above.--

Please replace the paragraph beginning on page 9, line 8, with the following rewritten paragraph:

--Favoured linkers of the tartaric acid series above can be generically depicted as Formula IIe:

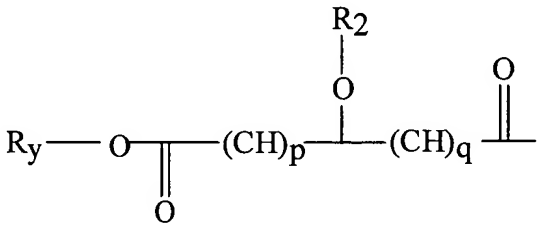


IIe

and isomers where R_1 and R_2 are reversed, where R_1 and R_2 are as shown above, p, q and r are each independently 0 to 5, preferably 0 or 1 and R_y is the free acid, an R_1 ester or a conventional pharmaceutically acceptable carboxy protecting group, such as the methyl, benzyl or especially the ethyl ester.--

Please replace the paragraph beginning on page 9, line 20, with the following rewritten paragraph:

-- Favoured linkers of the malic series have the formula IIf:



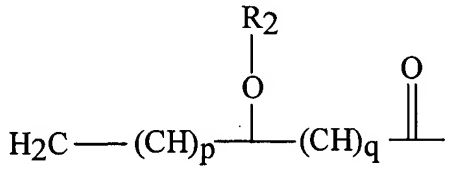
IIf

where Ry, p,q and R_2 are as defined above, preferably those where p and q are zero.--

Please replace page 12 with the following rewritten page 12:

--example on the β-carbon. In this embodiment the fatty acid of R_1 is esterified directly on the 5'-hydroxy (or equivalent) function of the nucleoside, generally with the R_2 group already esterified/amide bonded thereon. Alternatively, the functionalised fatty acid (the carboxy/hydroxy/amino function being appropriately protected) can be first esterified to

the nucleoside and deprotected prior to coupling with R_2. Linkers in accordance with a preferred embodiment of this aspect have the formula IId:



IId

where R_2 is the residue of an aliphatic L-amino acid and, p is 0, 1 or 2-20 (optionally including a double bond) and q is 0-5, preferably 0. Representative compounds include:

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-butyryl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-hexanoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-octanoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-decanoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-dodecanoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-myristoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-palmitoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-stearoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-docosanoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-eicosanoyl] guanosine

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-butyryl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-hexanoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-octanoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-decanoyl] guanosine,

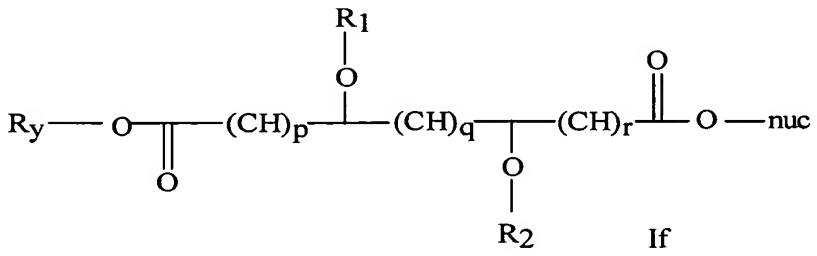
2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-dodecanoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-myristoyl] guanosine,

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-palmitoyl] guanosine,--

Please replace the paragraph beginning on page 21, line 1, with the following rewritten paragraph:

--

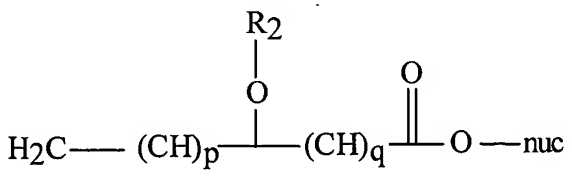


If

where R_1, R_2, R_y, p, q, r and o-nuc are as defined above.--

Please replace the paragraph beginning on page 22, line 1, with the following rewritten paragraph:

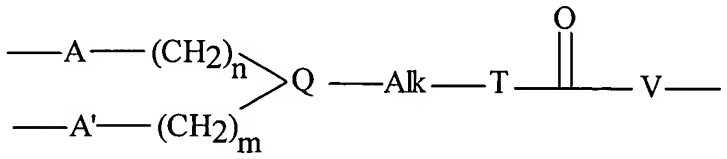
-- The invention also extends to compounds of the formula Ig



Ig

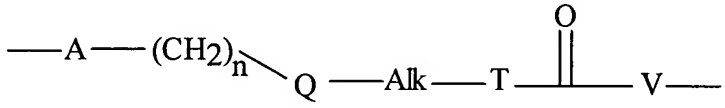
where R_2, p, q and O-nuc are as defined above.--

Please replace the paragraph beginning on page 43, line 1, with the following rewritten paragraph:



IIaa

B8

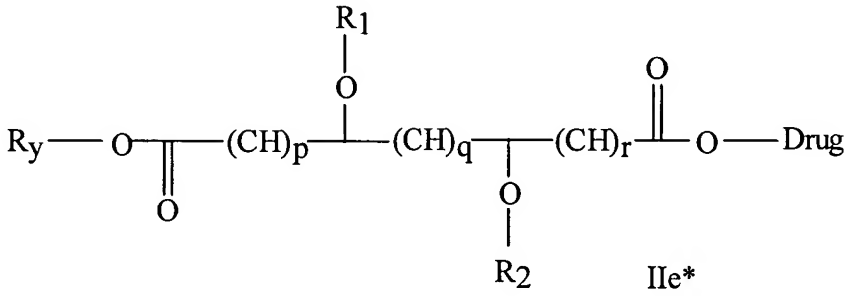


II'aa

where A and A' are independently--

Please replace the paragraph beginning on page 44, line 11, with the following rewritten paragraph:

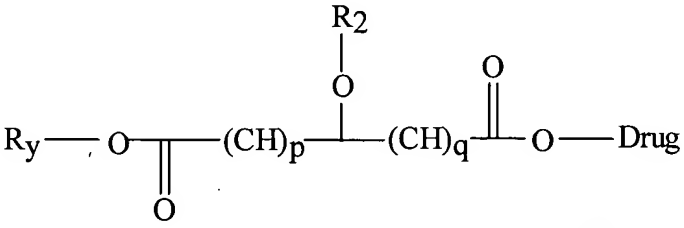
--formula II e*, that is



IIe*

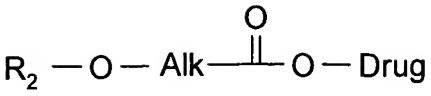
B9

formula II f*, that is



IIf*

Formula Id*, that is



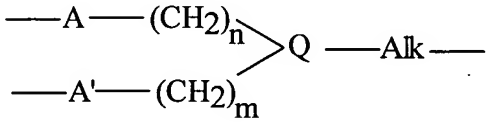
Id*

B9 con. -

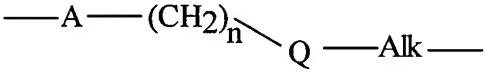
Please replace page 45, with the following rewritten page:

-- Where the Drug comprises a carboxyl function, the linker may comprise a structure of the formulae VIII or VIII':

where A, A', Q, Alk, m, and n are as defined for Formula IIaa & II'aa.



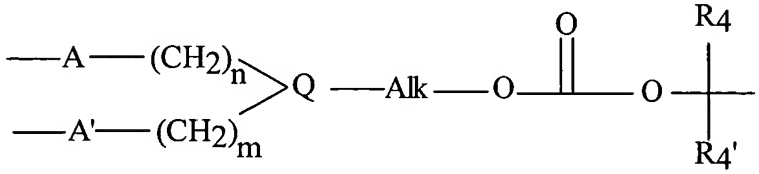
VIII



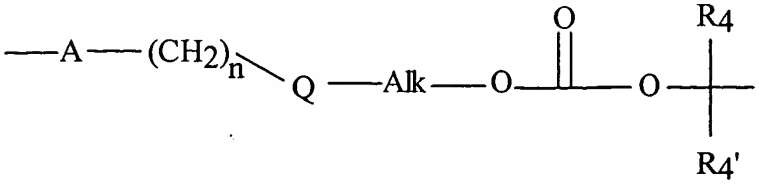
VIII'

B10

Preferably, however, when the Drug comprises a carboxy function, the di- or trifunctional linker group L is a structure of Formulae IIdd or II'dd (that is a compound of Formulae IIaa or II'aa, wherein T is O and V is a structure of the formula IIbb):



IIdd



II'dd

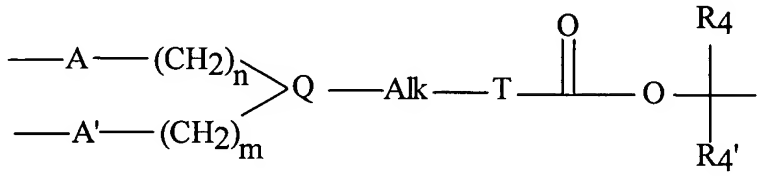
B10 Cont.

In structure IIdd, R_4' is preferably hydrogen and R_4 is ethyl, phenyl, and especially methyl or hydrogen or R_4 and $R_{4'}$ together define isopropyl--

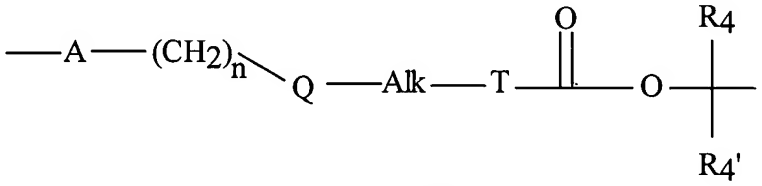
Please replace page 46, with the following rewritten page:

-- Where the Drug comprises a phosphoryl, phosphinyl or phosphonyl function, the di- or trifunctional linker group L may comprise a structure of the formula IIaa or II'aa, especially those of the formula IIee or II'ee:

B11



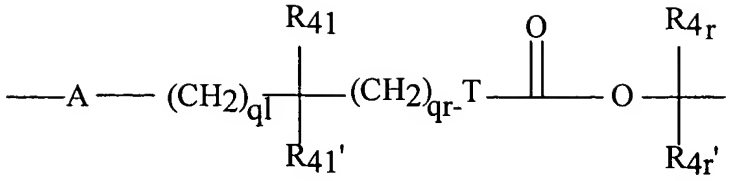
IIee



II'ee

where T is a bond, -NH- or -O- and Q and A are as defined above including the cyclic Q structures such as cycloalkyl, phenyl and heterocycles such as furyl, pyridyl etc. In structures IIee and II'ee, R_4' is preferably hydrogen and R_4 is methyl, ethyl, phenyl and especially hydrogen or R_4 and $R_{4'}$ define isopropyl.

Preferably, however, where the Drug comprises a phosphonyl, phosphinyl or phosphoryl function, the difunctional linker comprises a structure of the formula II"b:



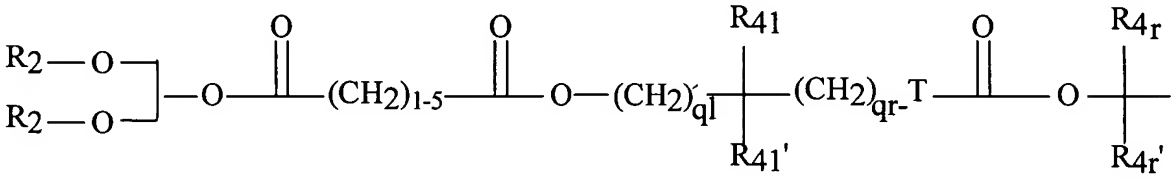
II"b

B11 cont.

where T is a bond, -O- or -NH-, R_{4l} R_{4r} and R_{4l}' and R_{4r}' are independently H or C_1-C_3 alkyl and A is as defined above (or wherein A is a further difunctional linker to--

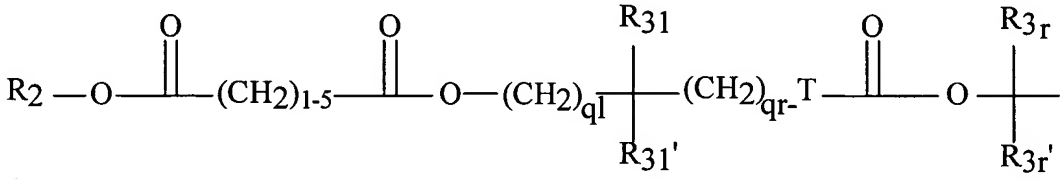
Please replace the paragraph beginning on page 47, line 1, with the following rewritten paragraph:

-- which one or more R_2 depends as described above). Examples of structures belonging to the latter possibility for A include those of Formula Va and Vb:



Va

B12

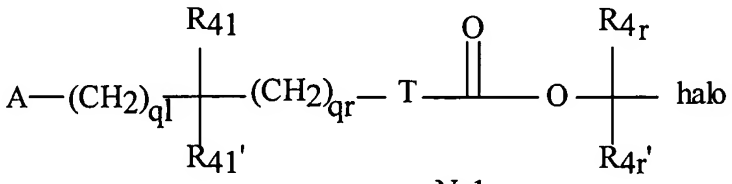


Vb

where T, q, R_2, R_{4l} R_{4l}' R_{4r} and R_{4r}' are as defined above. Although formulae Va and Vb depict the dicarboxylate moiety as unbranched, it will be apparent that a wide variety of dicarboxylates will be suitable here, including branched and/or unsaturated and/or substituted dicarboxylic acid derivatives or various lengths, as described in more detail above.--

Please replace the paragraph beginning on page 48, line 23, with the following rewritten paragraph:

-- A further aspect of the invention comprises novel intermediates useful in applying structures of the formulae II"b to a drug and having the formula N-1:

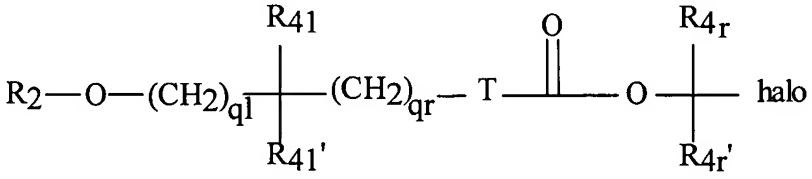


N-1

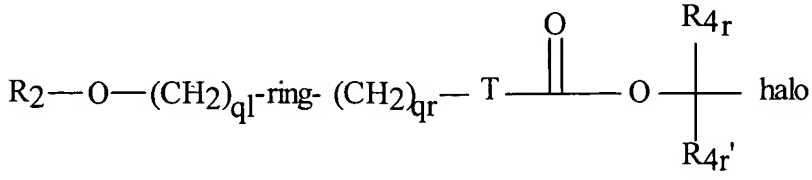
where A, q, R_4, R_4' and T are as defined for formula II"b.--

Please replace the paragraph beginning on page 49, line 1, with the following rewritten paragraph:

-- A particularly preferred group of compounds substantially within formula N-1 are those of the formula N-2



or



N-2

where

R_2 is the acyl residue of an aliphatic amino acid,

$R_{3L}$and R_{3L}' are independently H, C_{1-3} alkyl, C_{3-6}cycloalkyl, C_{1-3}alkyl-C_1C_6cycloalkyl phenyl or benzyl,

R_{3R} and R_{3R}' are independently H or C_{1-3} alkyl

ql is 0-3, qr is 0-3,

T is a bond, -NR_3- or -O-

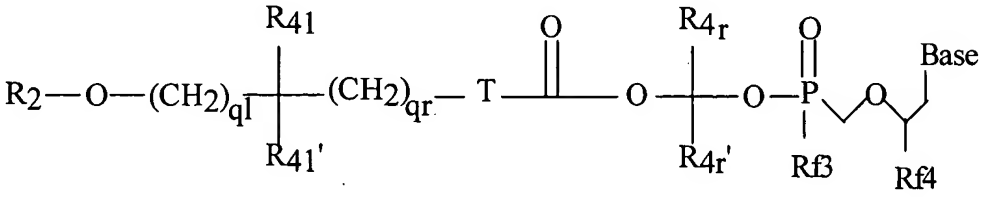
R_3 is H or C_{1-3}alkyl;

"ring" is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle; and

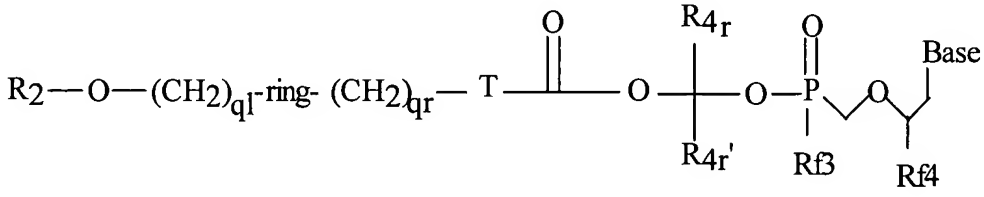
halo is bromo, chloro or iodo. --

Please replace the paragraph beginning on page 61, line 1, with the following rewritten paragraph:

-- Taking the phosphonate antivirals adefovir and cidovir as examples, prodrugs of the invention can be applied as shown in Formula PF2:



or



where

R_2 is the acyl residue of an aliphatic amino acid,

$R_{4L}$and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6}cycloalkyl, C_{1-3}alkyl-C_1C_6cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl

ql is 0-3, qr is 0-3,

T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

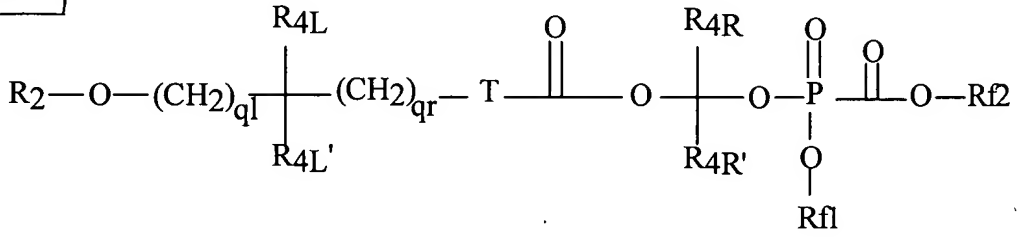
ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;

base is a natural or unnatural nucleotide base, especially guanine, adenine or cytosine,

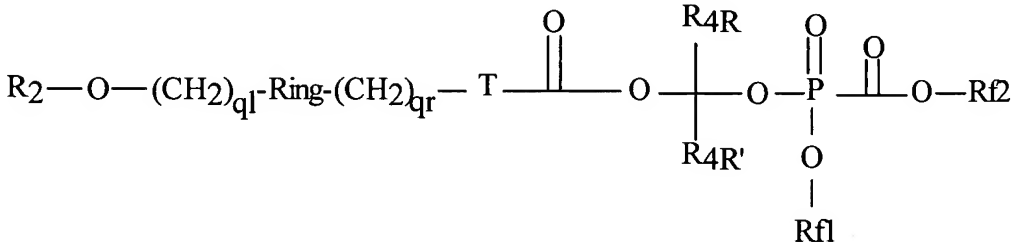
Rf3 is H or a further structure of the formula II"b and Rf4 is H or CH_2OH.--

Please replace the paragraph beginning on page 65, line 1, with the following rewritten paragraph:

--



or



where

R_2 is the acyl residue of an aliphatic amino acid,

$R_{4L}$and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6}cycloalkyl, C_{1-3}alkyl-C_1C_6cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl

ql is 0-3, qr is 0-3,

T is a bond, -NR_4- or -O-

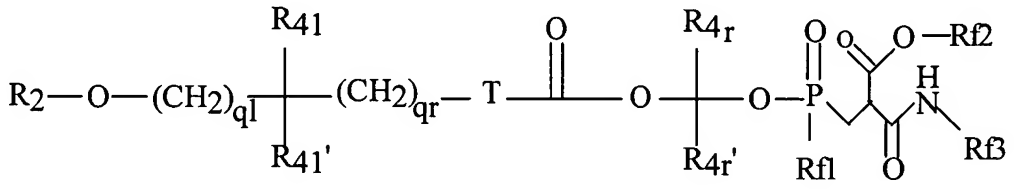
R_4 is H or C_{1-3}alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;

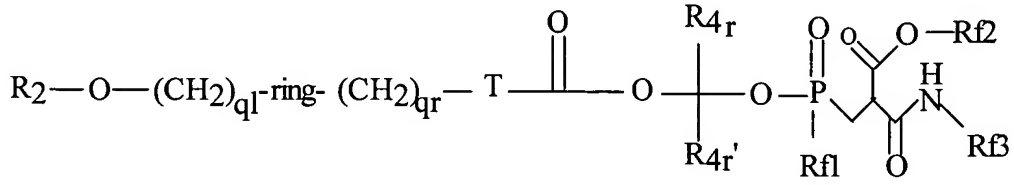
and Rf1 is H or a further ester of formula II"b and Rf2 is H or a conventional pharmaceutically acceptable ester.--

Please replace the paragraph beginning on page 68, line 1, with the following rewritten paragraph:

--



or



where RF1 is H or a further structure of formula II"b

Rf2 is H or a conventional pharmaceutically acceptable ester,

Rf3 is a polyunsaturated, branched C_{6-22} alkyl,

R_2 is the acyl residue of an aliphatic amino acid,

$R_{4L}$and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6}cycloalkyl, C_{1-3}alkyl-C_1C_6cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl

ql is 0-3, qr is 0-3,

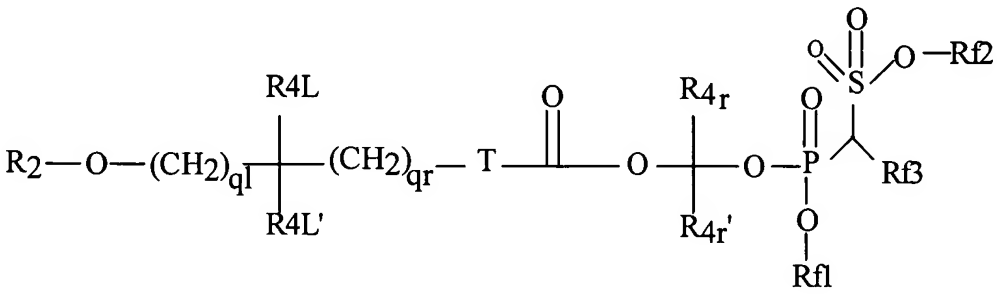
T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

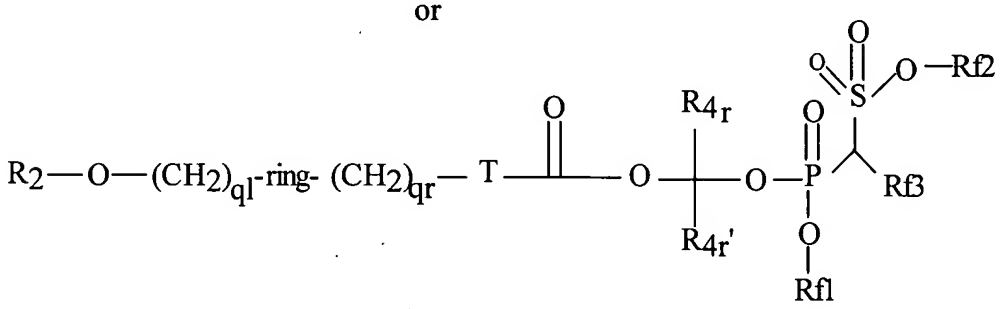
ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle.--

Please replace the paragraph beginning on page 69, line 4, with the following rewritten paragraph:

-- Other structurally similar phosponates include α-phosphonosulphonates such as squalene synthase inhibitors of the formula PF5:



or



where RF1 is H or a further structure of formula II"b

Rf2 is H or a conventional pharmaceutically acceptable ester a further structure of formula II"b

Rf3 is a polyunsaturated, branched C_{6-22} alkyl,

R_2 is the acyl residue of an aliphatic amino acid,

$R_{4L}$and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6}cycloalkyl, C_{1-3}alkyl-C_1C_6cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl

ql is 0-3, qr is 0-3,

T is a bond, -NR_4- or -O-

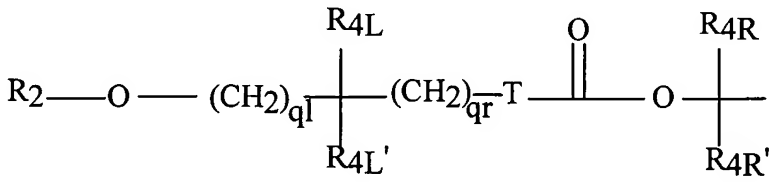
B18 cont.

R_4 is H or C_{1-3}alkyl;

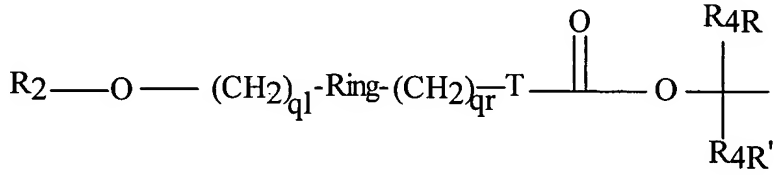
ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle.--

Please replace the paragraph beginning on page 73, line 1, with the following rewritten paragraph:

--



or



B19

where

R_2 is the acyl residue of an aliphatic amino acid,

$R_{4L}$and R_{4L}' are independently H, C_{1-3} alkyl, C_{3-6}cycloalkyl, C_{1-3}alkyl-C_1C_6cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R}' are independently H or C_{1-3} alkyl

ql is 0-3, qr is 0-3,

T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;

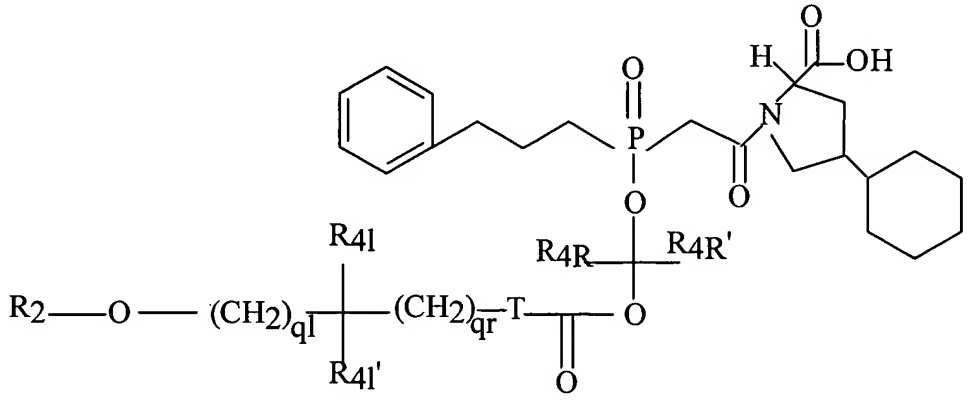
B19 cont.

and the remainder of Ra1-4 are hydrogen or conventional pharmaceutically acceptable esters.--

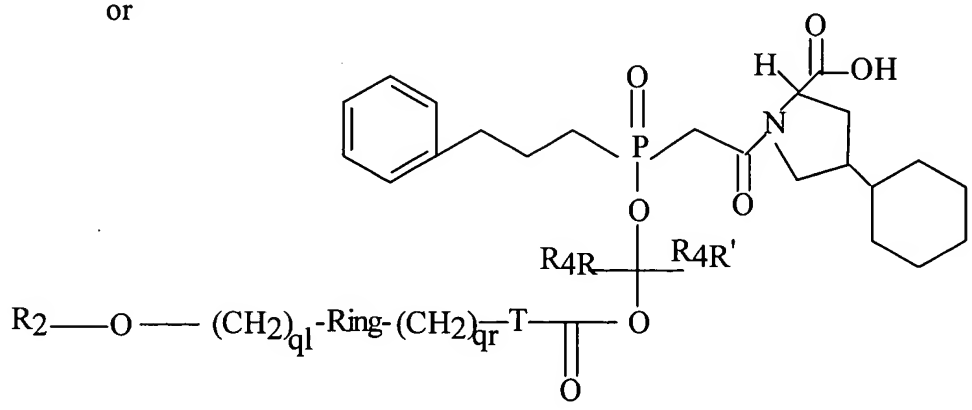
Please replace the paragraph beginning on page 85, line 16, with the following rewritten paragraph:

--A still further preferred group of prodrugs of the invention are those based on fosinoprilate having the formula PF3:

B20



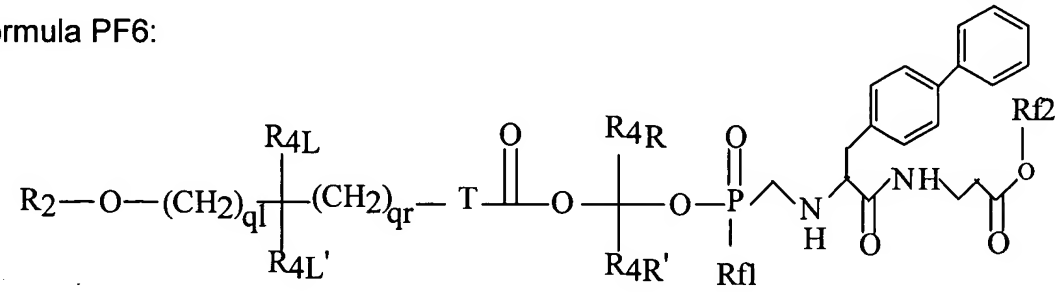
or



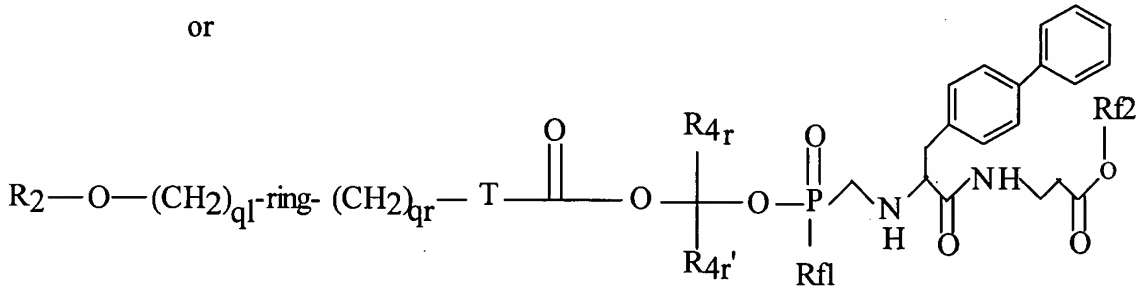
--

Please replace the paragraph beginning on page 88, line 13, with the following rewritten paragraph:

-- A further phosphonate compound amenable to the prodrugs of the invention are the neutral endopeptidase inhibitors such as CGS-24592 (Novartis), preferably those of the formula PF6:



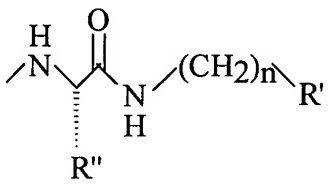
or



where RF1 is H or a further structure of formula II"b --

Please replace the paragraph beginning on page 100, line 21, with the following rewritten paragraph:

-- Disclosed embodiments of Formula II for the A'/A" groups of the compounds of formula I include those of the formula IIa:



IIa

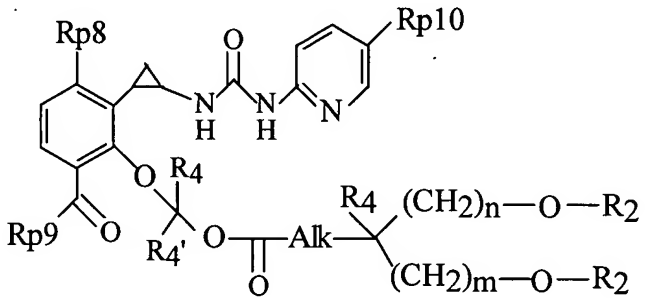
where n is 1 or 2 and R' is alkyloxy, preferably methyloxy, or those where n is 0 and R' is methyl.--

B22 cont

Please replace the paragraph beginning on page 130, line 18, with the following rewritten paragraph:

-- One variant of a branched Alk^b in Formula P5 can be substituted with hydroxy which in turn is esterified with a further R^2, thus defining a linker of the formula IIa, as depicted in Formula P6:

B23



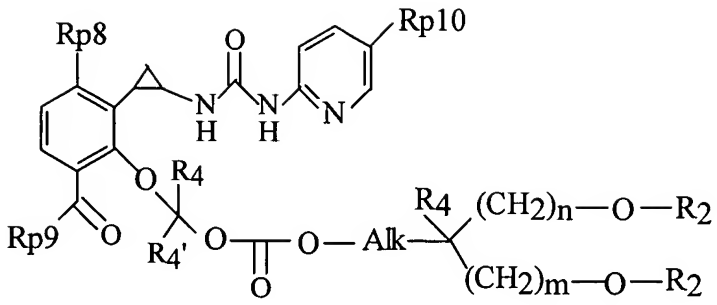
P6

where Rp8, Rp9, Rp10, Alk, R_4, R_4', m, n and R_2 are as defined above. Preferably each occurrence of Rx and Rx' is H. Particularly favoured values for Alk, m and n include: methylene:1:1 and absent: 1:0 respectively.--

Please replace the paragraph beginning on page 131, line 1, with the following rewritten paragraph:

-- A further favoured group of compounds has the Formula P7:

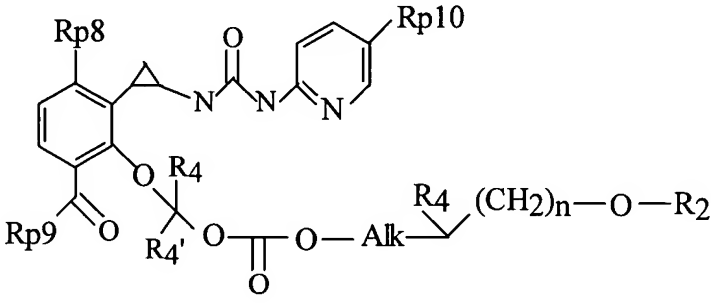
B24



P7

where Rp8, Rp9, Rp10, Alk, R_4, R_4', m, n and R_2 are as defined above or wherein the -()$_m$-O-R_2 arm is absent. Preferably each occurrence of Rx and Rx' is H. Particularly favoured values for Alk, m and n include:absent:1:1, thus defining a glycerol derivative. Where the -()$_m$-O-R_2 arm is absent to define a structure of the formula P7':

B24 cont.



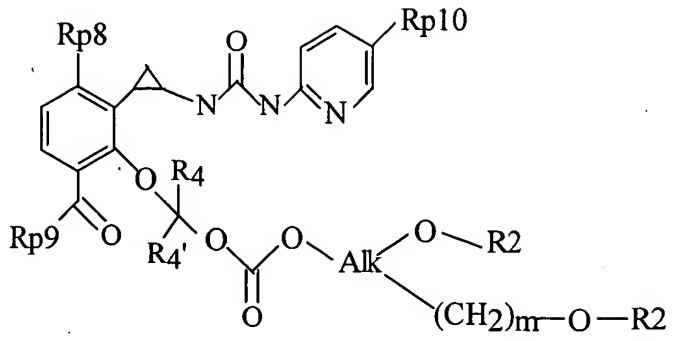
P7'

Convenient values for Alk and n include absent:1 with R_4, R_4 and R_4' as H.--

Please replace the paragraph beginning on page 134, line 2, with the following rewritten paragraph:

-- As with Formula P5/P6 and P7/P7', Alk^b in formula P8 can comprise an additional -O-R_2 substitution to define a compound of the formula P8'

B25

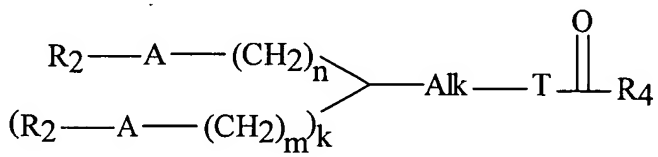


P8'

where each of the variables is as defined above.--

Please replace the paragraph beginning on page 138, line 18, with the following rewritten paragraph:

-- A still further aspect of the invention provides novel R_2 bearing linkers suitable for derivatisation to free functions on a Drug. Preferred linkers in accordance with this aspect of the invention include compounds of the Formulae IVa:



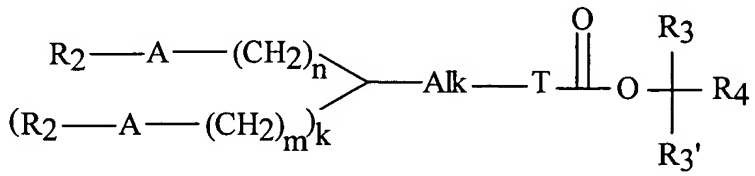
IVa

where R_2, A, A', n, m, Q, Alk, k and T are as defined above and R_4 is hydroxy or an activating group such as an acid derivatives including the acid halide, such as the chloride, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinamide derived esters, N-hydroxyphthalimide derived esters, N-hydroxy-5-norbornene- 2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived

esters and the like. Compounds of Formula IVa will be particularly useful for Drugs bearing hydroxy or amine functions.--

Please replace the two consecutive paragraphs beginning on page 139, line 1, with the following rewritten paragraphs:

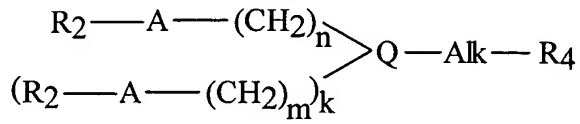
--Further preferred linkers in accordance with this aspect of the invention include compounds of the formulae IVe:



IVe

where R_2, A, A', n, m, Q, Alk and T are as defined above, and R_4 an activating group such as a halide, including bromo, chloro and iodo. Compounds of Formula IVe will be especially useful for Drugs bearing carboxy functions (especially those where T is O, R_3 is Me and R_3' is H) or phosphonyl functions (especially those where T is a bond, R_3 is isopropyl and R_3' is H).

Alternative preferred di- or trifunctional linker compounds of this aspect of the invention include compounds of the Formulae IIIa:



IIIa

where R_2, A, A', n, m, Q and Alk are as defined above and R_4 is hydroxy or an activating moiety such as halo, including chloro, iodo and bromo.--